Translational PKPD modeling in schizophrenia

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Population Pharmacokinetic-Pharmacodynamic Modelling of Haloperidol in Patients with Schizophrenia using Positive and Negative Syndrome Rating Scale

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Submitted

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CHAPTER 5

ABSTRACT

The aim of this study was to develop a pharmacokinetic-pharmacodynamic (PKPD) model that quantifies the efficacy of haloperidol, accounting for the placebo effect, the variability in exposure-response, and the dropouts. Subsequently, the developed model was utilized to characterize an effective dosing strategy for using haloperidol as a comparator drug in a future antipsychotic drug trial. The time course of plasma haloperidol concentrations from 122 subjects and the Positive and Negative Syndrome Scale (PANSS) scores from 473 subjects were used in this analysis. A non-linear mixed effects modelling approach was utilized to describe the time course of PK and PANSS scores. Bootstrapping and simulation-based methods were used for the model evaluation. A two-compartment model adequately described the haloperidol PK profiles. The Weibull and E_{max} model were able to describe the time course of the placebo and the drug effects, respectively. An exponential model was used to account for dropouts. Joint modelling of the PKPD model with dropout model indicated that the probability of patients dropping out is associated with the observed high PANSS score. The model evaluation results confirmed the precision and accuracy of parameter estimates to be acceptable. Based on the PKPD analysis, the recommended oral dose of haloperidol to achieve a 30% reduction in PANSS score from baseline is 5.6 mg/day and the corresponding steady-state effective plasma haloperidol exposure is 2.7 ng/ml. In conclusion, the developed model describes the time course of PANSS scores adequately and a recommendation of haloperidol dose was derived for the future antipsychotic drug trials.

INTRODUCTION

Haloperidol, a typical antipsychotic, was the most widely used drug for many years in the treatment of patients with schizophrenia and other psychotic disorders.[1] Haloperidol is still widely used as the prototypical comparator antipsychotic for randomized controlled trials (RCTs). The optimum dose of haloperidol is still not known, which is a problem when it is used as a comparator drug.[2] McEvoy et al.[3] recommended about 3 mg/day, whereas Van Putten et al.[4] found that the efficacy increased with doses up to 20 mg/day. The American Psychiatric Association guideline recommends a broad range of 5–20 mg/day[5] for the acute and the maintenance treatment of schizophrenia symptoms. Recently, Giegling et al.[6] discussed a statistical strategy for choosing an appropriate dose and the corresponding exposure of haloperidol for clinical studies based on the observed response. However, the observed inter-individual variability in the pharmacokinetics and pharmacodynamics of haloperidol was not fully characterized due to the small sample size of patients. To our knowledge, there is no literature available on population-based pharmacokinetic-pharmacodynamic (PKPD) modelling of haloperidol using the PANSS total score that would help in determining the effective haloperidol dose. Hence, in the present study we developed a PKPD model that describes the time course of the PANSS total scores accounting for the contributors to the variability in the haloperidol exposure-response. Subsequently, a methodology for an effective dosing strategy (which dose and corresponding effective exposure?) when haloperidol is used as a comparator drug in future clinical trials is described. In order to achieve these goals, we applied a non-linear mixed effects modelling approach to describe the population pharmacokinetics (POP-PK) of haloperidol. Consequently, the developed POP-PK was used as an input model for building the PKPD model that describes the time course of PANSS total score accounting for the placebo effect, the variability in exposure-response, and the dropouts. Furthermore, the developed PKPD model was utilized to quantify the efficacy of haloperidol for the PANSS subscales with the aim of investigating the hypothesis of better negative symptom control by atypical antipsychotics than conventional antipsychotics, but the results of this analysis will be published elsewhere.

MATERIALS AND METHODS

Participants and Study Design

In total data from 515 patients were used to develop and to evaluate the PK and PKPD model. The overview of the datasets with their trial design, patient demographics, summary statistics of the PANSS scores, and dropout rates across the studies used in the development of the PKPD model are shown in table 1. In brief, the population PK model for haloperidol was developed from seven studies, with data from

TABLE 1: Summary of datasets used for the population-based of PK and PKPD analysis

	Dataset: PK model		
Reference	**Population**	**Dose, dosage regimen**	**PK sampling**
7	7 schizophrenic patients (Age 20-32 years)	Fixed dose of 2 mg/day, multiple dosing	12-14 hours post dose
8	5 schizophrenic patients (Age 21-43 years)	Fixed dose of 1-5 mg/day, multiple dosing	12-14 hours post dose
9	4 schizophrenic patients (Age 22-42 years)	Flexible dose of 3-60 mg/day, multiple dosing	18-20 hours post dose
10	6 schizophrenic patients (Age 18-29 years)	Flexible dose of 4-12 mg/day, multiple dosing	6 hours post dose
11	16 healthy male volunteers (Age 18-38 years)	Fixed dose of 3 mg/day, single dose	Rich sampling up to 24 hours
12	4 healthy male volunteers (Age 26-39 years)	Flexible dose of 2-7.5 mg/day, single dose	Rich sampling up to 27 hours
6	80 schizophrenic patients (Age 18-64 years)	Flexible dose of 2.5-40 mg/day, multiple dosing	~1-2 hrs post dosing

Dataset: PKPD model												
Study	**Trial Phase**	**Study Duration**	**ROA**	**Disease type**	**Age (years)**	**Gender F:M**	**Race (White: Black: Hispanic: Asian/ other)**	**Dose (mg)**	**#Subjects**	**Median baseline PANSS**	**PANSS Change from baseline**	**Dropout (%)**
INT-2*	III	8 weeks	Oral/ BID	Chronic	37 (19-68)	76:150	184: 15: 16: 11	5	226	87	-14.8	28
INT-3*	III	8 weeks	Oral/ BID	Chronic	37.5 (18-64)	13:69	61: 15: 3: 3	7.5	82	93	-5.0	60
128-115#	III	6 weeks	Oral/ BID	Acute	37 (18-69)	25:60	57: 24: 0 : 4	7.5	85	94	-15.0	44
LMU	Open	4 weeks	Oral/QD	Acute	34 (18-64)	35:45	80: 0: 0: 0	2.5-40	80	106	-41.8	42

ROA: route of administration; **BID**=twice daily; **QD**: once daily; **F**: female; **M**=male.
Haloperidol was used as an active comparator in Risperidone*and Ziprasidone # clinical trials from Janssen and Pfizer respectively.

122 individuals [healthy volunteers (n=20) and schizophrenic patients (n=102)] and 538 plasma concentrations obtained from a wide dose range of 1 to 60 mg/day administered either as a single or multiple doses. On the other hand, PANSS data from four studies in 473 schizophrenic patients with 2342 PANSS observations were utilized to describe the exposure-response relationship of haloperidol.

Model Development

A non-linear mixed effects modelling (NONMEM) approach to describe the time course of PK and PANSS scores was implemented using the NONMEM VII software[13] (ICON Development Solutions, USA). Perl-speaks-NONMEM[14] (PsN, v 3.2.4) was used to operate NONMEM. R (version 2.11; *www.r-project.org*) was used for graphical inspection of the results. Log-transformed plasma haloperidol concentrations were used to estimate the PK parameters, while absolute PANSS scores were used for the PD model. The First-Order Conditional Estimation (FOCE) method with or without interaction option in NONMEM was used to estimate PK and PKPD model parameters. FOCE along with the Laplace approximation method in NONMEM was utilized for estimating the dropout model parameters.[15]

Inter-individual variability (IIV) for the structural model parameters was evaluated using a log-normally or a normally distributed model:

$$P_j = PTV \times exp^{(\eta j)} \text{ or } P_j = PTV + \eta_j$$

where PTV represents the population typical value of the parameter and P_j is the value of the parameter for subject j. ηj denotes an individual-specific random effect that distinguishes the value of the j^{th} subject from the PTV. The values of η_j are assumed to be normally distributed with mean zero and and variance ω^2. Inter-individual variability is expressed as percent coefficient of variation (% CV).

The intra-individual or residual variability (RUV) describes the error terms, which remain unexplained and refers to, for example, dosing inaccuracies, analytical assay error, or error in recording sampling times, and structural model misspecifications.

A proportional error model was used to describe RUV in the plasma concentration, while, an additive term was used to account for the unexplained variability in PANSS score as shown in the following equations:

$$ln(y_{ij}) = ln(\hat{y}_{ij}) + \varepsilon_{ij} \quad \text{for PK model}$$

$$y_{ij} = \hat{y}_{ij} + \varepsilon_{ij} \quad \text{for PD model}$$

where y_{ij} is the j^{th} observation in the i^{th} individual, $\hat{y}_{ij}$ is the corresponding model prediction, and ε_{ij} is a normally distributed random error with a mean of zero and a variance of σ^2.

Model selection was based on comparison of the objective function values (ΔOFV: 3.84, corresponding to a p value of 0.05) and the goodness-of-fit (GOF)

plots. Goodness-of-fit was assessed graphically by evaluation of the agreement between observed and predicted plasma concentrations or PANSS scores, the range of conditional weighted residuals (CWRES), and uniformity of the distribution of CWRES about zero across the range of the predicted concentrations or PANSS scores. The percentage relative standard errors (% RSE) of the parameter estimates and reductions in both IIV and RUV were also used to discriminate between competing models. The ΔOFV and Kaplan-Meier-based visual predictive check plots were used to choose the best dropout model.

Influences of patient and study specific covariates were evaluated as possible explanatory variables for the variability in the PK or PKPD model parameters. Covariate analysis was performed in NONMEM using PsN with a step-wise forward additive approach followed by a step-wise backward elimination approach with a p value of 0.05 and 0.01, respectively.[14] Uncorrelated covariates were included in the model using different functional forms like linear, piece-wise linear, power and exponential functions.

Population Pharmacokinetic Analysis

One- and two-compartment models with first-order absorption and with or without absorption lag-time were evaluated. Pre-specified subroutines (ADVAN2 or 4) in the NONMEM software were used to model the time course of haloperidol exposure. The available covariates were tested for their influence on clearance (CL/F) and central volume of distribution (Vc/F). It is fair to assume that the measure of clearance relates to drug exposure and varies between individuals because of identifiable patient characteristics. If the CL/F value was not influenced by any of the covariates, a fixed allometric relationship with individual body weight as the adjustment of CL/F to body size: CL/F=TVCL*[weight/70]**$^{0.75}$ was used as a covariate. For patients in whom pharmacokinetics were not assessed or available, the population-based PK parameter estimates from POP-PK model were used for the predictions of PK profile.

Pharmacokinetic-Pharmacodynamic Model

As a first step in building the exposure-response relationship, a placebo model that was developed and validated previously,[16] was incorporated into the drug effect model such that the pharmacological effectiveness of the drug was estimated on top of the placebo effect.

The Weibull placebo model was used to account for the placebo effect. Previously reported predictors of variable placebo effect were included in the final PKPD model.[16]

The treatment effect was modelled as a relative change from the baseline PANSS score as shown in the below equation.

$$\text{PANSS Score} = \text{Baseline PANSS} \times \left[\left(1 - P_{max} \times \left(1 - e^{-\left(\frac{time}{TD}\right)^{POW}}\right)\right) * \left(1 - \left(\frac{E_{max} \times C_{ss}}{EC_{50} + C_{ss}}\right) * \left(1 - e^{-KT \times time}\right)\right)\right]$$

where P_{max} is the maximum placebo effect, TD is the time to reach 63.2% of maximum change in PANSS from baseline, POW is the shape parameter, E_{max} is the maximum drug effect, Css is the patient-specific average steady-state plasma concentration which was estimated using the dose, dosing interval, bioavailability, and the Bayesian estimate of CL/F values obtained from the final POP-PK model: [C_{ss} = dose/CL/F/dosing interval]. We assume that C_{ss} is constant over the study period, as little fluctuation in the exposure can be anticipated once a patient reaches steady-state levels (i.e. after 5-6 half-lives) and most PANSS observations were done at steady-state conditions. EC_{50} is the steady-state concentration required to achieve 50% of E_{max}, and KT is a rate constant associated with the time required to obtain the maximum drug effect. IIV for baseline PANSS and EC_{50} was assumed to be log-normally distributed. Normally distributed IIV was used for P_{max} and E_{max} parameters, which allows the placebo and drug effect to be positive (improvement, i.e. decrease of PANSS score) or negative (worsening, i.e. increase in PANSS score). All the parameters that were described in the above equation were estimated except 2 placebo model parameters, namely, POW and TD which were fixed, based on our earlier results.[16] The covariates of the placebo effect and of the dropout rates (supplementary file 1) were fixed during the subsequent PKPD modelling. We extended the use of the developed PKPD model to the PANSS subscales (i.e. positive and negative subscales) accounting for their respective placebo effects (unpublished data).

To predict the mean changes in the PANSS adequately, it was necessary to account for the dropouts. The exponential time-to-event (TTE) dropout model was used jointly with the PD model. The probability of a patient dropping out from a trial can be predicted by describing the hazard for the dropout event. Hazard is the instantaneous rate of the dropout event: h(t).

$$h(t)=BHAZ\times \exp(-\text{predictor} \times BETA)$$

The model assumes that baseline hazard (BHAZ) is independent of time, and estimates the BHAZ and BETA as dropout model parameters. BHAZ is baseline hazard without influence of predictors, while BETA is a parameter that describes the probability of a patient dropping out based on the predictors such as observed PANSS score, unobserved (predicted), unobserved (predicted) + observed PANSS, change in the PANSS score from baseline, or drug exposure. Several predictors can be included within the TTE model structure with parameterzing different BETAs for each of the predictors. Cumulative hazard (CHZ) predicts the risk of a patient dropping out from the study over the time interval, which is obtained by integrating the hazard over time. The probability of survival (not dropping out) can be predicted from the cumulative hazard: S(t)=exp(-CHZ). Finally, the probability of dropping out at time t is given by D(t)=S(t)×h(t). The best predictor(s) of dropout was selected based on the ΔOFV. A sequential approach[17,18] was used to estimate the dropout model parameters conditioning on the estimates of the PKPD model.

Model Evaluation

The developed PK and PKPD models were evaluated by bootstrap analysis and simulation-based methods within the NONMEM software using PsN.[14] One thousand bootstrap datasets were obtained by re-sampling with replacement from the original haloperidol dataset with stratification based on study, and then the final model was fitted to each of the bootstrapped datasets. The bootstrap median and 2.5th & 97.5th percentiles were obtained for each parameter from the distribution of parameter estimates from successful NONMEM estimation runs. These were compared with the estimates obtained from the original dataset.[19,20] The other model evaluation method used was the Stochastic Simulation and Estimation (SSE), which is a simulation-based tool for evaluating model appropriateness and adequacy. The final model was used to generate a number of simulated datasets, which were subsequently fit to this input model. The median parameter estimates of the simulations were compared to the final parameter estimates from the input model. The accuracy of parameter estimates was measured by computing the % bias [Bias =100%*mean (estimated parameter-true parameter)/true parameter].

Monte-Carlo simulations were performed for the final PK and PKPD model to construct the visual predictive check plots (VPC). In brief, 1000 datasets identical in structure to the original PK and PKPD dataset were simulated, using the parameter estimates and inter- and intra-individual variability from the respective final models. Separate VPC plots were plotted for both the PK and PKPD model after calculating the 2.5th, 50th and 97.5th percentiles of plasma concentrations or PANSS scores for the simulated datasets.

With respect to visual predictive checks of the PK model, a VPC plot was constructed only for the Ludwig Maximilians University (LMU) study where the steady state plasma haloperidol concentrations were available.

For the PKPD model, initially, simulations were performed for the base PKPD model (without dropout model and predictors of placebo effect). Subsequently, simulations for the final PKPD model were performed along with the dropout model + predictors of placebo effect, in which the observed PANSS scores were replaced with the simulated PANSS scores from the final PKPD model. Then, VPC plots were plotted separately for different studies after calculating the 2.5th, 50th and 97.5th percentiles of PANSS scores for the simulated datasets.

Calculations of the Haloperidol Therapeutic Dose and Concentrations

Calculations of the haloperidol therapeutic dose and plasma concentrations based on the final PKPD model using PANSS total scores are discussed below. PANSS scores corresponding to the targeted % change was calculated based on the following equation correcting for minimum possible PANSS total score of 30.

$$\%\ \text{chage in PANSS Total} = \frac{\text{PANSS} - \text{Baseline PANSS}}{\text{Baseline PANSS} - 30} \times 100$$

Rearranging the above equation,

PANSS = - (% change in PANSS total/100)*(Baseline PANSS - 30) + Baseline PANSS

The corresponding PANSS value is obtained using the estimate of baseline PANSS from the final PKPD model and knowing the desired % change in PANSS score from baseline.

e.g. with a targeted 30% reduction from baseline with a baseline PANSS score of 90:

PANSS = -(30/100)*(90 -30) + 90 will yield a PANSS score of 72.

Above calculated PANSS was then plugged into the equation describing the change in score from baseline in our PKPD model: PANSS= Baseline PANSS *(1-Placebo effect)*(1-Drug effect). Assuming maximum (at the end of the trial) placebo and drug effect, the equation becomes

PANSS= Baseline PANSS $\times(1-P_{max})\times(1-E_{max}\times C_{eff}/(C_{eff}+EC_{50}))$.

After rearrangement of the above equation we obtain the steady-state effective concentration (C_{eff}) necessary to reach the targeted PANSS score:

$C_{eff}= EC_{50}/(E_{max}/(1-PANSS/(\text{Baseline PANSS}\times(1-P_{max})))-1)$.

The corresponding therapeutic dose is calculated using the following relationship Effective dose (mg/day)=C_{eff}*CL/F. The above calculations were also extended to PANSS subscales.

RESULTS

Haloperidol Pharmacokinetic Analysis

Haloperidol pharmacokinetics following oral administration was best described by a two-compartmental model with first-order absorption. The appropriateness of the two-compartment over the one-compartment PK model was based on the visual comparison of goodness-of-fit (GOF) plots (Figure 1; top panel) and the lower objective function value. The ADVAN4 TRANS4 subroutines and the FOCE estimation method with interaction option in NONMEM were used to estimate the two-compartment PK model parameters. The final population pharmacokinetic parameters for haloperidol are shown in table 2. IIV could only be estimable for CL/F and Vc/F. The unexplained variability (RUV) in the PK model was 44%. None of the patient-related covariates in our dataset influenced the population

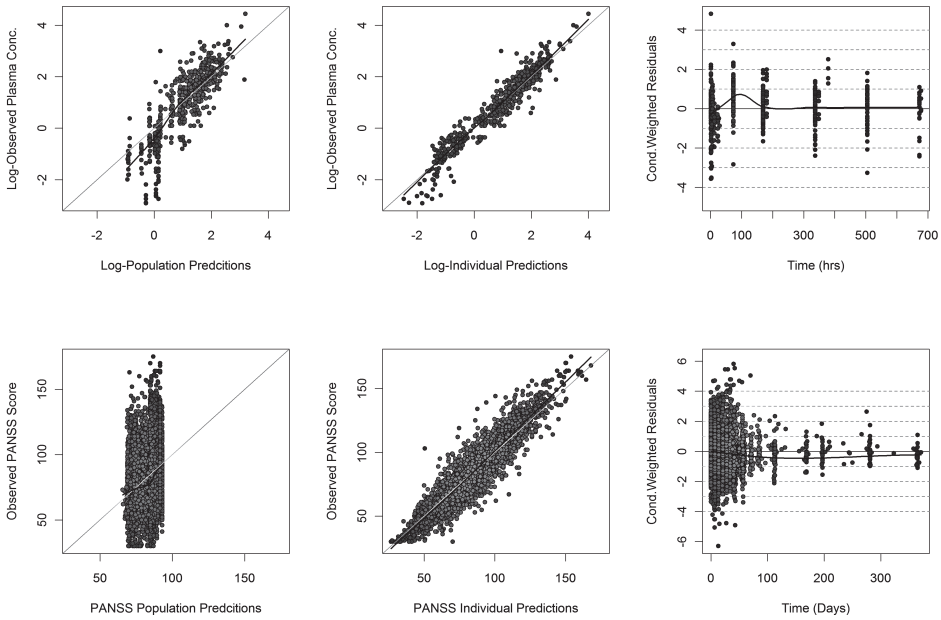

Fig. 1. *Goodness-of-fit-plots of the haloperidol final PK (top panel) and PKPD model (bottom panel)*

typical PK parameters at the p-level of 0.05. The median parameter estimates obtained from the 985 successful bootstrap replicates of the PK data were within 5% of those obtained with the final PK model and the original data set. Median values of the parameter estimates from the SSE analysis are in most cases in good agreement with the model-estimated original value. The bias in the parameters estimates were less than 12% for all the PK parameters. A representative VPC plot following 1000 simulations based on the final PK model is shown in figure 2a.

Haloperidol Pharmacokinetic-Pharmacodynamic Analysis

An E_{max} model was used to quantify the drug effect. In order to quantify the exposure-response relationship of haloperidol, a patient-specific steady-state plasma concentration was used. The placebo effect (P_{max}) for a typical schizophrenic patient was estimated to be 0.081 (i.e. the maximum relative decrease in PANSS from the baseline PANSS score was 8.1%). Similarly, the maximum drug effect (E_{max}) of haloperidol was found to be 0.31 (i.e. the maximum relative decrease in PANSS score from baseline following haloperidol treatment on top of the placebo effect was 31%). The typical EC_{50} value for PANSS total was found to be 3.58 ng/ml. The inter-individual variability of EC_{50} parameter (152 %CV) was found to be relatively large in our analysis. This high variability may also include the part of the variability arising from pharmacokinetics (such as differences in bioavailability, variable first-pass effect and dosing inaccuracies).

Table 2: Summary of haloperidol final PK model and model evaluation results

Parameters	Original Dataset (% RSE)	Bootstrap Results	SSE Results	
		Median (95% CI)	Median	% Bias
Pharmacokinetic Model				
CL/F (L/h)	88 (6)	89 (77-101)	86	-2
Q/F (L/h)	233 (28)	225 (56-391)	250	12
Vc/F (L)	669 (29)	637 (91-1143)	700	9
Vp/F (L)	2500 (39)	2487 (573-3565)	2715	12
Ka (hr^{-1})	0.236 (18)	0.227 (0.056-0.387)	0.235	6
IIV-CL (% CV)	44.5 (13)	44 (31-55)	44	-0.5
IIV-Vc (% CV)	116 (14)	119 (95-180)	122	-5
RUV proportional	0.44 (3)	0.44 (0.38-0.50)	0.44	-6
Pharmacokinetic-Pharmcodynamic Model				
Baseline PANSS	91.6 (1)	91.6 (90.8-92.3)	91.7	0.5
P_{max}	0.081 (9)	0.075 (0.064-0.096)	0.083	4
E_{max}	0.31 (20)	0.34 (0.19-0.66)	0.29	-2
EC_{50} (ng/ml)	3.58 (39)	4.03(1.89-10.78)	2.71	-15
KT (1/day)	0.116 (4)	0.113 (0.062-0.167)	0.12	6
$t_{½}$ (delay in drug effect, in days)*	6	-	-	-
BHAZ: Placebo (1/day)	0.00139 (9)	0.00144 (0.0009-0.0015)	0.00139	0.1
BHAZ: Haloperidol (1/day)	0.0009 (9)	0.00087 (0.00066-0.00111)	0.0009	0.1
BETA	-0.0295 (2)	-0.0292 (-0.0317--0.0271)	-0.0292	-0.2
IIV P_{max} (SD)	0.20 (4)	0.20 (0.19-0.22)	0.21	-0.2
IIV Baseline PANSS (CV %)	16 (4)	16 (15-17)	16	-1
IIV E_{max} (SD)	0.29 (35)	0.28 (0.17-0.48)	0.27	-7
IIV EC_{50}(CV %)	152 (48)	151 (76-287)	138	16
RUV as SD (additive)	8.7 (1)	8.7 (8.3-9.1)	8.6	0.1

RSE = relative standard error**; SSE** = Stochastic Simulation and Estimation; **CL/F** = apparent clearance; **Q/F** = inter-compartmental clearance; **Vc** = central volume of distribution; **Vp** = peripheral volume of distribution; **ka** = absorption rate constant; **CV** = coefficient of variation; **IIV** = inter-individual variability; **RUV** = residual unexplained variability; **P_{max}** = maximum placebo effect; **E_{max}** = maximum drug effect; EC_{50} = concentration to achieve 50% of E_{max}; KT = rate constant to account for delay in drug effect; **SD** = standard deviation; **BHAZ** = baseline hazard, **BETA** = parameter relating hazard to PANSS score. *Calculated using equation t½ =0.693/K. The IIV shrinkage values were less than 20% except for EC_{50}(>50%). The RUV shrinkage was 16.2%. The accuracy (bias %) in parameter estimation by the SSE method is computed as = 100 × mean (estimated parameter-true parameter)/true parameter. % CV = $\sqrt{\omega^2}$*100

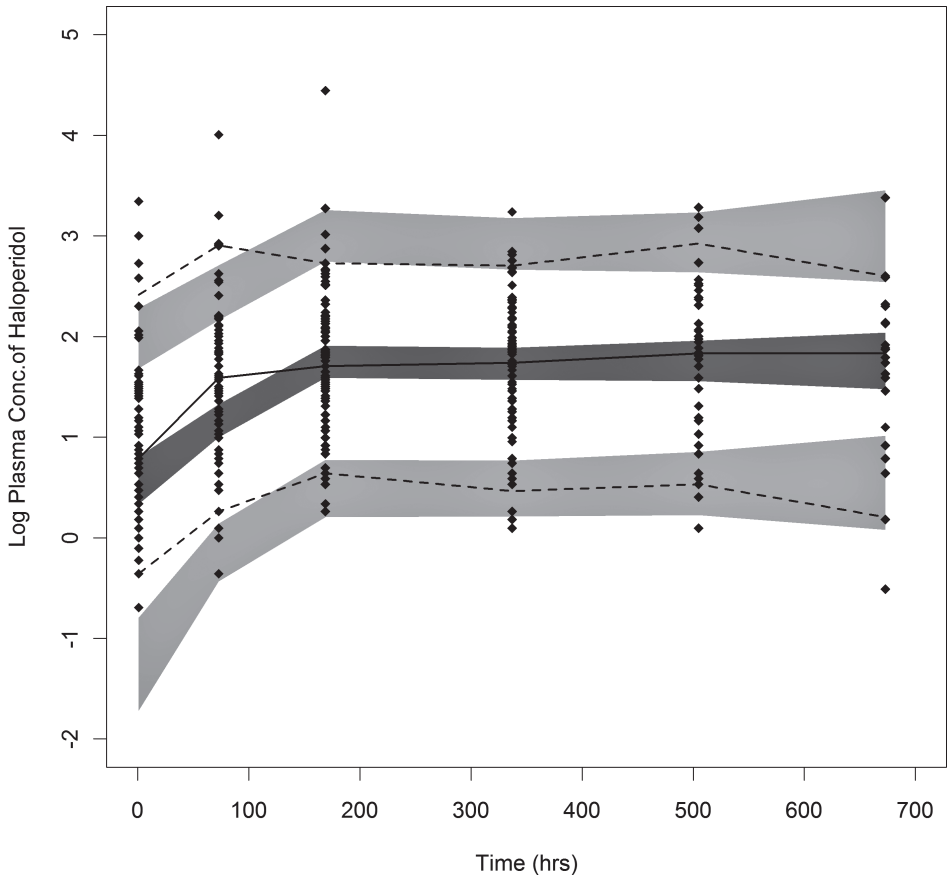

Fig. 2a. *A representative visual predictive check (VPC) plot (Ludwig Maximilians University study) of the haloperidol final PK model. The grey shaded areas represent the 95% confidence intervals of the corresponding 2.5th, 50th and 97.5th percentiles of the simulated data, the black dashed represents the 2.5th, 97.5th percentiles of the observed data and the black solid line represents the median of the observed data. Dots represents observed haloperidol conc.*

To investigate the effect of IIV-EC_{50} on the precision of the PD parameter estimates, we compared the models with estimating IIV-EC_{50}, and fixing IIV-EC_{50} at 50 CV%. The PD parameter estimates (E_{max} and EC_{50}) were found to be comparable with similar precision. Hence, based on ΔOFV value, we choose the PKPD model with estimating the IIV-EC_{50} for further model evaluation steps.

The bootstrap results from the 957 successful runs are shown in table 2. The difference between the median parameter estimates obtained from the successful bootstrap replicates of the PKPD data and those obtained with the final PKPD model with the original data set were less than 2.5%. Moreover, the final parameter estimates from the developed model were well within the bootstrap

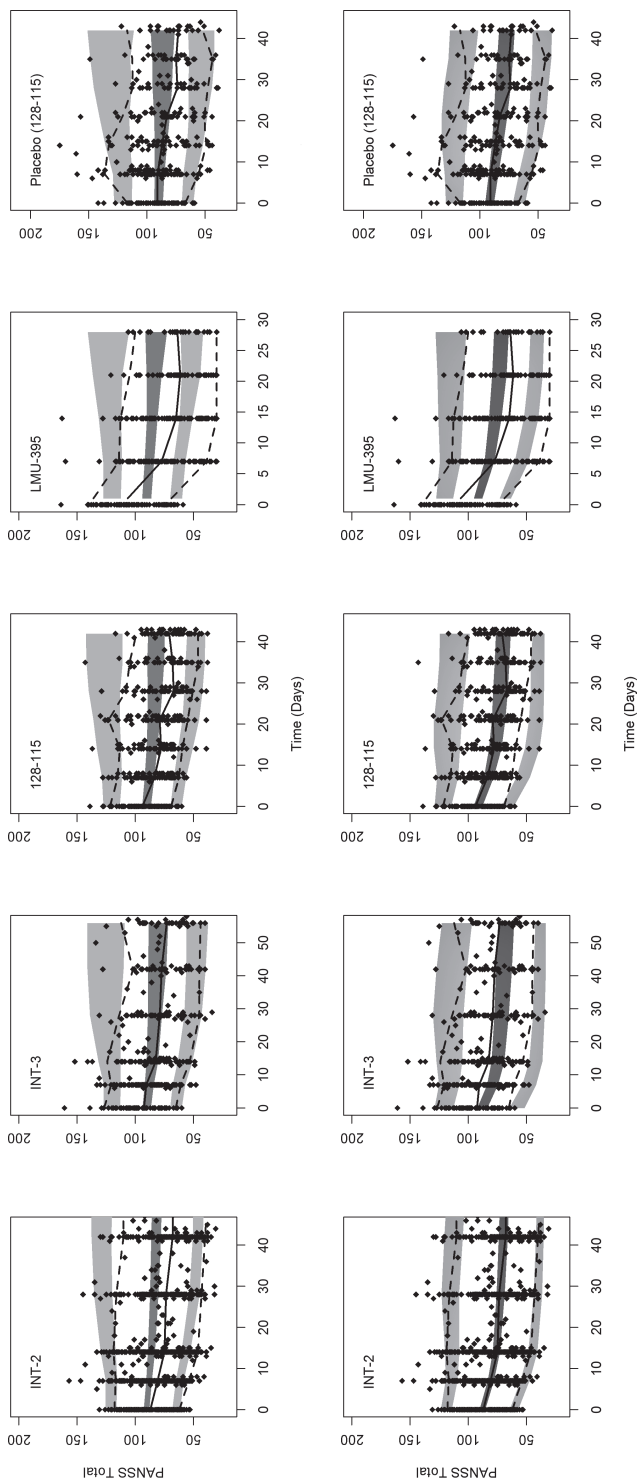

Fig. 2b. *Visual predictive check (VPC) plots of the haloperidol final PKPD model.* ***Top panel****: base model and* ***bottom panel****: final PKPD model accounting for the dropouts and predictors of placebo response. The grey shaded areas represent the 95% confidence intervals of the corresponding 2.5th, 50th and 97.5th percentiles of the simulated data, the black dashed represents the 2.5th, 97.5th percentiles of the observed data and the black solid line represents the median of the observed data . Dots represents observed PANSS scores.*

95% CI. Simulation-based (SSE) results indicated that PKPD model parameters were estimated precisely (table 2).

We extended the use of the developed PKPD model to the PANSS subscales. The model was able to describe the time course of positive and negative symptoms adequately without any further modification. The predictors of the placebo effect (unpublished data) for both symptoms were also accounted in the model. The efficacy of haloperidol (E_{max}) for positive symptoms was approximately twice that of negative symptoms (0.48 vs. 0.21), respectively and the corresponding EC_{50} values were 1.28 and 6.39 ng/ml (Table 3). The parameter estimates of both subscales were estimated precisely with % RSE less than < 35%.

A dropout model based on the observed PANSS score was selected for further evaluation. The BHAZ parameter describing the hazard of a patient dropping out at baseline levels of covariates or predictors may be different for different treatments, hence we estimated separate BHAZ for the placebo and the haloperidol treatment.

The estimates of BHAZ for placebo and haloperidol were found to be 0.0014 and 0.0009, respectively. The BETA parameter which describes the hazard of a patient dropping out from a trial based on the observed PANSS irrespective of treatment was estimated to be -0.0295. The value -0.0295 indicates that probability of a patient dropping out from a trial increased exponentially with increasing PANSS score. Monte-Carlo simulations were performed along with the combined PANSS + dropout model + covariates, in which the observed PANSS scores were replaced with the simulated PANSS scores from the final PKPD model after accounting for dropouts and its predictors (figure 2b; bottom panel). When dropout was ignored, the simulations showed wide prediction intervals at the end of the study, while the actual observed percentile intervals were much narrower (figure 2b; top panel). When the dropout model was included in the simulations,

Table 3: Calculated effective haloperidol dose and concentrations for PANSS total, PANSS positive and PANSS negative subscales at 30% reduction in score from baseline

	PKPD model estimated parameters				Effective Conc. in ng/ml (C_{eff})	Corresponding dose: Effective dose (mg/day)=Css×CL/F
	Baseline score	P_{max}	E_{max}	EC_{50}		
PANSS total	91.6	0.081	0.31	3.6	2.7	5.6
PANSS positive subscale	23.4	0.099	0.41	1.2	0.54	1.2
PANSS negative subscale	24.1	0.047	0.21	6.4	31	65

C_{eff}= EC_{50}/(Emax/(1-PANSS/(Baseline PANSS×(1-Pmax)))-1); % change in score is given by = PANSS -Baseline PANSS/(Baseline PANSS- number of PANSS items*); *number of PANSS items: PANSS total: 30; PANSS positive: 7; PANSS negative: 7

the simulated prediction intervals were in close agreement with those of the observed percentile intervals indicating that patients, who had higher PANSS or, worsening of disease condition, had dropped out before the end of the trial.

DISCUSSION

In clinical practice and drug development, an understanding of the exposure–response relationship is crucial for the efficient determination of a suitable therapeutic range for the majority of patients. Population pharmacokinetic modelling has been used in analyzing data from clinical trials, as well as data derived from routine clinical practice.[21] This approach has the advantage of incorporating all patient-related covariates into the PKPD model whereas the conventional non-compartmental approach of pharmacokinetic analysis considers these factors as a burden for data analysis and hence to be controlled.[20] The non-linear mixed-effects modelling approach allows analyzing the data of all individuals at once and considers inter- and intra-individual random effects. This ensures that confounding correlations and disparity that may occur in observational data are properly accounted for.[22]

So far, no population-based PKPD model is available for haloperidol. The aim of this study was to develop a PKPD model that quantifies the efficacy of haloperidol, accounting for the placebo effect and dropouts. Subsequently, the developed PKPD model was utilized to characterize an improved dosing strategy (which dose and related exposure?) for using haloperidol as a comparator drug in future antipsychotic drug trials or observational clinical studies.

The current data analysis utilized pooled data from 3 RCTs and 1 open-label clinical study which consists of heterogeneous populations including Caucasians, Black, Asian, and Hispanic people. The parameter estimates from the PK model were comparable to those reported in Japanese patients by Yukawa et al.[23] None of the tested demographic covariates had a significant effect on haloperidol disposition. However, we used a fixed allometric relationship with individual body weight as the adjustment of clearance to body size. The paucity of PK information in the dataset could have masked the influence of covariates on haloperidol disposition. Nevertheless, Yukawa et al.[23] reported that haloperidol oral clearance in Japanese patients was affected by four covariates, namely body weight, age, dose, and anti-epileptic drug co-medication. Therefore, the effect of covariates in patients from another race/ethnicity (e.g. Caucasians) cannot be ruled out completely. We did not have plasma measurements from the chronic patients and Css for these patients were calculated based on the population PK model adjusted to the patient's body weight, dose, and dosage regimen. Hence, we did not succeed in quantifying the influence of covariates on the drug effect parameters such as EC_{50}. Due to the lack of information about reduced haloperidol, i.e. main metabolite of haloperidol, metabolite kinetics was not included in our

PK model. However, evidence suggests that the antipsychotic effect in acute schizophrenic patients is mainly due to parent drug and there is no additional contribution of reduced haloperidol.[24] Hence absence of metabolite kinetics in our PK model may be of less concern while estimating the PD parameters.

Haloperidol has a high affinity (K_i) to dopamine D_2 receptors (0.7 nM) and a slow rate of dissociation (0.017 min^{-1})[25] while it has a low affinity to other receptors like 5-HT_{2A}, D_1, and D_3.[26] Due to these pharmacological properties it is hypothesized that haloperidol may exhibit lower efficacy towards the negative symptoms.[25] We used the final PKPD model to characterize the efficacy of haloperidol towards the PANSS positive and negative symptoms. Haloperidol exhibited a lower E_{max} for negative symptoms over positive symptoms; this finding is in line with the hypotheses that the negative symptoms do not only depend on dopaminergic hyperactivity and the involvement of other receptors plays an important role in exhibiting a better efficacy towards the negative symptoms.

At present, the PANSS total score is more commonly used than the Brief Psychiatric Rating Scale. Thus, an investigation was performed using the PANSS score as a clinical endpoint to estimate the precise therapeutic dose or exposure range of haloperidol required in the clinic. Haloperidol exposure to produce a 30% change in PANSS total score from baseline PANSS was found to be 2.7 ng/ml (table 3) which is in agreement with the effective mean concentration of haloperidol of 3.82 ng/ml as reported by Giegling et al.[6] The corresponding dose for a 30% change in PANSS score from baseline PANSS was found to be 5.6 mg/day.

To characterize the relationship between the clinical efficacy and D_2 receptor occupancy (D_2RO) levels, we used the following relationship: $D_2RO=D_{max}*C_{eff}/(ED_{50}+ C_{eff})$. Where, D_{max} is the maximum receptor occupancy attributable for a given haloperidol exposure, ED_{50} is the plasma level of haloperidol associated with 50% of D_2RO. The values of ED (0.32 ng/ml) and D_{max} (84%) were directly obtained from a recent article by Uchida et al.[27] while, the C_{eff} is calculated value (2.7 ng/ml) from our final PKPD model was used in the above equation to calculate mean D_2RO. The PKPD model-estimated haloperidol EC_{50} value relates to 75% D_2RO which is in close agreement with the presumed D_2RO therapeutic window of 65-80%.[28,29]

In the standard statistical analysis the estimation of drug effect may be influenced by the high placebo effect and the high dropout rate. We used a model-based normalized placebo effect[16] after accounting for the predictors of placebo response to quantify the drug effect. In addition, we demonstrated that joint modelling of drug effect and dropout should be considered while quantifying the true drug effect (figure 2b; bottom panel). The limitation of this work is that we mainly focused on linking the exposure to the efficacy parameters, however, an additional support for this choice of dose by linking the exposure to safety parameters (e.g. modelling of extrapyramidal side effects) to further optimize the therapeutic dose range of haloperidol is in progress. In conclusion, based on our

data analysis, the haloperidol recommended dose if used as a comparator in clinical trials with diverse schizophrenic patients to achieve a good clinical effect is 5.6 mg/day and the corresponding plasma haloperidol exposure is found to be 2.7 ng/ml.

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REFERENCES

1. Kudo S, Ishizaki T. Pharmacokinetics of haloperidol - An update. Clin Pharmacokinet 1999; 37(6):435-456.
2. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009; 373(9657):31-41.
3. McEvoy JP, Schooler NR, Wilson WH. Predictors of Therapeutic Response to Haloperidol in Acute Schizophrenia. Psychopharmacol Bull 1991; 27(2):97-101.
4. Vanputten T, Marder SR, Mintz J. A Controlled Dose Comparison of Haloperidol in Newly Admitted Schizophrenic-Patients. Arch Gen Psychiatry 1990; 47(8):754-758.
5. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J of Psy 2004; 161(2):1-56.
6. Giegling I, Drago A, Schafer M, et al. Interaction of haloperidol plasma level and antipsychotic effect in early phases of acute psychosis treatment. J Psychiatr Res 2010; 44(8):487-492.
7. Kapur S, Remington G, Jones C, et al. High levels of dopamine D-2 receptor occupancy with low-dose haloperidol treatment: A PET study. Am J Psychiatry 1996; 153(7):948-950.
8. Kapur S, Zipursky R, Roy P, et al. The relationship between D-2 receptor occupancy and plasma levels on low dose oral haloperidol: A PET study. Psychopharmacology 1997; 131(2):148-152.
9. Xiberas X, Martinot JL, Mallet L, et al. Extrastriatal and striatal D-2 dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. Br J Psychiatry 2001; 179:503-508.
10. Farde L, Nordstrom AL, Wiesel FA, et al. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. Arch Gen Psychiatry 1992; 49(7):538-544.
11. Liem-Moolenaar M, te Beek ET, de Kam ML, et al. Central nervous system effects of haloperidol on THC in healthy male volunteers. J Psychopharmacol 2010; 24(11):1697-1708.
12. Nordstrom AL, Farde L, Halldin C. Time course of D2-dopamine receptor occupancy examined by PET after single oral doses of haloperidol.

Psychopharmacology (Berl) 1992; 106(4):433-438.

13. Beal S, Sheine, LB, Boeckmann A, and Bauer RJ. NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009.
14. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit - A collection of computer intensive statistical methods for non-linear mixed effect modelling using NONMEM. Comput Methods Programs Biomed 2005; 79(3):241-257.
15. Beal SL, Sheiner LB, Boeckmann AJ. NONMEM Users Guides. Icon Development Solutions, Ellicott City, MD, 2010.
16. Pilla Reddy V, Kozielska M, Johnson M, et al. Modelling and simulation of the PANSS time course and dropout hazard in placebo arms of schizophrenia clinical trials. Clin Pharmacokinet 2012; 51(4):261-275
17. Zhang LP, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data I: Best-case performance. J Pharmacokinet Pharmacodyn 2003; 30(6):387-404.
18. Zhang LP, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data II: Robustness of methods. J Pharmacokinet Pharmacodyn 2003; 30(6):405-416.
19. Efron B. Bootstrap Confidence-Intervals for A Class of Parametric Problems. Biometrika 1985; 72(1):45-58.
20. Efron B. Better Bootstrap Confidence-Intervals. J Am Stat Assoc 1987; 82(397):171-185.
21. Wade JR, Sambol NC. Felodipine population dose-response and concentration-response relationships in patients with essential-hypertension. Clin Pharmacol Ther 1995; 57(5):569-581.
22. Ette EI, Williams PJ. Population pharmacokinetics II: Estimation methods. Ann Pharmacother 2004; 38(11):1907-1915.
23. Yukawa E, Hokazono T, Yukawa M, et al. Population pharmacokinetics of haloperidol using routine clinical pharmacokinetic data in Japanese patients. Clin Pharmacokinet 2002; 41(2):153-159.
24. Ulrich S, Neuhof S, Braun V, et al. Reduced haloperidol does not interfere with the antipsychotic activity of haloperidol in the treatment of acute schizophrenia. Int Clin Psychopharmacol 1999; 14(4):219-228.
25. Kapur S, Seeman P. Does fast dissociation from the dopamine D-2 receptor explain the action of atypical antipsychotics?: A new hypothesis. Am J Psychiatry 2001; 158(3):360-369.
26. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. CMAJ 2005; 172(13):1703-1711.
27. Uchida H, Takeuchi H, Graff-Guerrero A, et al. Predicting Dopamine D(2) receptor rccupancy from plasma levels of antipsychotic drugs a systematic review and pooled analysis. J Clin Psychopharmacol 2011; 31(3):318-325.
28. Kapur S, Zipursky R, Jones C, et al. Relationship between dopamine D-2 occupancy, clinical response, and side effects: A double-blind PET study of first-episode schizophrenia. Am J Psychiatry 2000; 157(4):514-520.
29. Nordstrom AL, Farde L, Wiesel FA, et al. Central D2-Dopamine receptor rccupancy in Relation to Antipsychotic Drug Effects - a Double-Blind Pet Study of Schizophrenic-Patients. Biological Psychiatry 1993; 33(4):227-235.